Unusual infections complicating diabetes

Professor Robert Tattersall

Today's diabetes world is fast-moving and exciting; knowledge is accumulating at an astonishing rate. To help understand the present, however, it sometimes helps to examine the past.

In this installment of *Tattersall's Tales*, Robert Tattersall outlines unusual infections that complicate diabetes, a history of their first recognition, their symptoms, prevalence in people with diabetes and their current management.

Unusual infections that complicate diabetes include necrotising fasciitis, emphysematous cystitis and pyelonephritis, malignant otitis externa, rhinocerebral mucormycosis and injection site infections, which are outlined below.

Necrotising fasciitis

Necrotising fasciitis is a rare, potentially fatal infection characterised by widespread necrosis of the subcutaneous tissue, superficial fascia and skin. In 1871 an army surgeon, Joseph Jones, wrote one of the earliest descriptions of necrotising soft-tissue infections in soldiers during the American Civil War and with a mortality rate of 46%. In one series between 1958 and 1970, three-quarters of the 63 patients had diabetes (Stone and Martin, 1972). In diabetes it is caused by a symbiosis between aerobic gram-negative bacteria and anaerobic bacteria, whereas in those without diabetes it is usually caused by *Streptococcus pyogenes*, which the press calls a "flesh-eating bacterium". It characteristically involves whole muscle compartments with little damage to the overlying skin and subcutaneous tissue. The surface lesion is often small and the exudate looks like dishwater. The amount of pain is often much greater than one would imagine it should be from physical examination. The relative surface normality can lead to underestimation of the extent of the gangrene and need for debridement. The most common sites are the pelvis and thigh, but in one of my patients, an elderly woman, a large area of her lower back became gangrenous.

A specific form of necrotising fasciitis is fulminating gangrene of the genitalia described in 1881 by the French venereologist Jean Alfred Fournier (1832–1914). Fournier (1883) noted that diabetes was a predisposing factor for gangrene in general, although none of his five patients had the disease. Fournier suggested several possible causes. For example, *Cantharides* ("Spanish fly") could cause prolonged erection "permitting acts of extraordinary erotic valour, and, under these circumstances the penis can become gangrenous." He also mentioned placement of a mistress' ring around the phallus and ligation of the prepuce (an attempted birth-control technique practised by an adulterous man to avoid impregnating his lover). Physicians, said Fournier, should ask their patients about "unavowed obscene practices". Reassuringly, he noted that ordinary sexual intercourse could not cause the condition, "otherwise we would see a great deal of it in our clinics."

In most series, up to 60% of patients have diabetes, most being middle-aged men. Before antibiotics the mortality was high – in a 1930 series, 27% and in a 1945 one 32.5% (Rudolph et al, 1975). There is often extensive loss of scrotal tissue so that the testes hang free like bell clappers; they are not involved because their blood supply comes from the spermatic arteries. Treatment is by extensive debridement and, since the scrotal skin rapidly regenerates, even large defects can be covered from scrotal remnants.

The most famous sufferer was probably King Herod the Great, who ruled Judea from 37 to 4 BC and whose final illness was described in great detail by the historian Josephus. Herod died at the age of 70, and the most prominent and distressing symptom of his final illness was "putrefaction of his privy member". Whether he had diabetes is unclear, but it is certainly possible as his disposition to overindulgence was well documented (Litchfield, 1998).

Emphysematous cystitis and pyelonephritis

Pneumaturia was first described in 1671, but until 1860 all cases reported involved fistulas between the bowel and bladder. In that year Adam Raciborski (1809–1871) was called to see a man who passed bubbles of gas from his urethra and named the condition pneumouria (Raciborski, 1860). In 1883 Firmin Guiard (1852–1920) and Charles Féré (1852–1907) first pointed out the occurrence of pneumaturia in diabetes and reported four cases (Guiard and Féré, 1883). In 1891 the celebrated German physician Hermann Senator (1834–1911) first recorded the association of pneumaturia with cystitis in patient with diabetes. He noted that the urine was acid and had the odour of a fermented yeast mixture; the gas was largely carbon dioxide and the fermented urine was highly alcoholic on distillation (Senator, 1891).

Over the subsequent 120 years there have been sporadic case reports, most of the recent ones being in radiology journals. The most common causative organisms are *Escherichia coli* and *Enterobacter aerogenes*. Most patients have diabetes, but it can occur with neuropathic bladders, bladder outlet obstruction and in-dwelling urinary catheters.

Emphysematous cystitis can be an incidental X-ray finding or cause a severe illness with dysuria, haematuria, pneumaturia, fever and abdominal pain. The radiological findings include small gas-filled vesicles in the bladder mucosa, producing a cobblestone appearance; there can also be a thin zone of gas outlining the perimeter of the bladder. Emphysematous cystitis usually responds well to antibiotics and glycaemic control, whereas emphysematous pyelonephritis is a more severe and life-threatening illness (Pontin et al, 1995). Most patients are women who are acutely ill with a high fever, dehydration and

often ketoacidosis. Historically, mortality has been as high as 50%; emergency nephrectomy used to be the treatment of choice, but some recent case reports have suggested that conservative treatment may be adequate.

Malignant otitis externa

In his first paper in 1968, James Chandler of the University of Miami described malignant otitis externa as "a particularly severe type of infection which tends to occur in the elderly diabetic patient. It results in unremitting pain, purulent discharge and tends to invade cartilage, bone, nerve and adjacent soft tissues" (Chandler, 1968). Of the 13 cases he reported only one, a 48-year-old woman, did not have diabetes; however, three with diabetes aged 35, 51 and 58 years were not exactly "elderly"! By 1972 when Chandler summarised his experience with 38 patients, 36 had frank diabetes although five had been diagnosed with a glucose tolerance test. The commonest complication, occurring in nearly half the patients, was facial palsy; about half with this complication in Chandler's series died. Hoarseness and aspiration from involvement of the tenth, eleventh and twelfth cranial nerves were even worse prognostic signs (Chandler, 1977).

In 1976 Zaky et al pointed out that most case reports had been in the ear, nose and throat (ENT) literature and that it was not well known to diabetes specialists, and this is still true today. The cause is *Pseudomonas aeruginosa,* and now the prognosis is much better, although treatment with ciprofloxacin may need to be prolonged for many weeks (Carfrae and Kessler, 2008).

Rhinocerebral mucormycosis

The classical report of three fatal cases of mucormycosis in individuals with diabetes in the USA was published in 1943 (Gregory et al, 1943). The patients were aged 43, 52 and 75 years, and the first two were admitted in ketoacidosis. Orbital swelling was present in all three at the time of admission, and at autopsy the meningeal vessels contained broad fungus filaments. Specimens were sent to the principal mycologist of the US Public Health Service, who thought the hyphae resembled those of *Mucor* – hence the name mucormycosis. Later it was realised that the fungus was actually *Rhizopus*, but it seems that it was too late to change the name. The authors did not speculate on the role of diabetes except to say that it was well known that there was a high incidence of fungal infections in people with diabetes. Surveys in the 1950s suggested that between 19 and 40% of cases occurred in people with diabetes – the rest being complications of leukaemia or cancer (Baker, 1960). The presentation is with headache, orbital or facial pain, fever and malaise. In individuals with poorly controlled diabetes, the infection can spread rapidly to the cavernous sinus and skull base and cause cranial nerve palsies.

Injection site infections

Injection site infections have always been uncommon, however poor the individual's hygiene and however many times a needle has been used. This is almost certainly because insulin preparations contain a preservative such as phenol or metacresol.

One unusual infection is that caused by *Mycobacterium chelonei var abscessus*. This organism was first isolated in 1903 from a turtle, and the first reported human infection was in 1953. In an outbreak in 1969, 12 people in County Durham were infected through histamine injections from multidose bottles at a local ENT clinic (Inman et al, 1969). More recently, outbreaks have been reported as a result of tattooing or mesotherapy – since you ask, mesotherapy is a treatment for cellulite (Inman et al, 1969; Regnier et al, 2009). The first case in a person with diabetes was reported in 1980 from Guy's Hospital, London, in a 24-year-old English woman (Jackson et al, 1980); a further diabetic case was reported in 1987 in an 18-year-old girl of Pakistani origin (Kelly, 1987). In a patient of mine the clinical appearance was of half-a-dozen deep, painful, lumps on her thighs and buttocks, which sometimes discharged a thin fluid. Repeated cultures were sterile, but after several weeks the laboratory rang me to say that a mycobacterium had been isolated. The organism is very slow growing in culture and is usually resistant to standard anti-tuberculous drugs *in vitro*. This was the case in my patient, although a 6-month course of rifampicin cured her.

Baker RD (1960) Diabetes and mucormycosis. *Diabetes* **9**: 143–4

Carfrae MJ, Kessler BW (2008) Malignant otitis externa. *Otolaryngol Clin N Am* **41**: 537–49

Chandler J (1968) Malignant external otitis. *Laryngoscope* **78**: 1257–94

Chandler JR (1977) Malignant external otitis: Further considerations. *Ann Otol* **86**: 417–28

Fournier JA (1883) Gangrène foudroyante de la verge. *Semaine Med* **3**: 345–8. Translated by: Corman AS (1988) Classic articles in colonic and rectal surgery. *Dis Colon Rectum* **31**: 984–8

Gregory JE, Golden A, Haymaker M (1943) Mucormycosis of the central nervous system. A report of three cases. *Bull Johns Hopkins Hosp* **73**: 405

Guiard FP, Féré C (1883) *Du Développement Spontané de Gaz dans la Vessie (Pneumaturie Diabétique).* JB Baillière et fils, Paris

Inman PM, Beck A, Brown AE, Stanford JL (1969) Outbreak of injection abscesses due to *Mycobacterium abscessus. Arch Dermatol* **100**: 141–7

Jackson PG, Keen H, Noble CJ, Simmonds NA (1980) Injection abscesses in a diabetic due to *Mycobacterium chelonei var abscessus. Br Med J* **281**: 1105–6

Kelly SE (1987) Multiple injection abscesses in a diabetic caused by *Mycobacterium chelonei. Clin Exp Dermatol* **12**: 48–9

Litchfield WR (1998) The bittersweet demise of Herod the Great. *J R Soc Med* **91**: 283–4

Pontin AR, Barnes RD, Joffe J, Kahn D (1995) Emphysematous pyelonephritis in diabetic patients. *Br J Urol* **75**: 71–4

Raciborski A (1860) Exemple de pneumaturie ou d'urine gazeuse chez une malade affecte d'nevropathie proteiforme avec predominance des symptoms de l'hypochondrie. *Gaz d Hopital Paris* **33**: 264–5

Regnier S, Cambau E, Meningaud JP et al (2009) Clinical management of rapidly growing cutaneous mycobacterial infections after mesotherapy. *Clin Infect Dis* **49**: 1358–64

Rudolph R, Soloway M, DePalma RG, Persky L (1975) Fournier's syndrome: Synergistic gangrene of the scrotum. *Am J Surg* **129**: 591–6

Senator H (1891) Ueber pneumaturie im allgemeinen un bei diabetes mellitus insbesondere. *Internat Beit z Wissenschaft Med* **3**: 317

Stone HH, Martin JD (1972) Synergistic necrotising cellulitis. *Ann Surg* **175**: 703–11

Zaky DA, Bentley DW, Lowy K et al (1976) Malignant external otitis: A severe form of otitis in diabetic patients. *Am J Med* **61**: 298–302